REMARKS

I. Status of the Claims

Claims 1, 5-8, 16 and 17 are pending. Upon entry of this amendment, claims 1 and 16 are amended simply to delete references to non-elected subject matter (i.e., PDZ proteins other than TIP-1 and PL proteins other than LPAP). Claims 7 and 8 are amended so they are no longer dependent upon a canceled claim. Thus, none of these amendments are made for reasons of patentability. New claim 18-20 are also introduced upon entry of this amendment. These claims are supported throughout the specification including, for example, by original claim 1, and at page 1, lines 16-19, page 5, lines 19-20 and page 28, lines 27-29.

II. Drawings

Formal drawings addressing the objections of the draftsperson are enclosed.

III. Claim Rejections under 35 U.S.C. 112, First Paragraph

Claims 1, 5-8 and 16-17 are rejected because the specification is alleged not to enable one of skill in the art to make or use the claimed invention. The Office Action provides primarily three reasons for reaching this conclusion: 1) the specification does not disclose that either LPAP or TIP-1 are expressed in endothelial cells, 2) the function of LPAP is unknown, and 3) uncertainty in view of the results presented in the application on the particular PL sequences capable of binding the PDZ protein TIP-1. Applicants respectfully disagree with these conclusions and will address them in turn.

With regard to the first issue, it is noted that endothelial cells are mesoderm-derived cells that form, for example, the lining of blood vessels and lymphatic channels. In the case of LPAP, Ding et al. (Eur. J. Immunol. 29:3956-61, 1999; copy enclosed) indicate that LPAP is associated with lymph nodes, thus providing evidence of the expression of LPAP in certain endothelial cells. A search of human ESTs corresponding to TIP-1 indicates that it is expressed in several types of endothelial cells including, for example: 1) placenta (see, e.g., gi30289553 and gi30217506), 2) uterine cervix - highly vascularized (gi28096580); and 3)

lymph node (see, e.g., gi19201531). Copies of the foregoing GenBank listings are provided. These ESTs are indicative of expression in both lymphatic channels and vascular lining. It is also noted that certain claims are limited specifically to hematopoietic cells (e.g., claims 8, 17, 18 and 20). This particular concern does not apply to these claims.

The Office Action also states that the claims are not enabled because of uncertainty regarding the function of LPAP. In this application, an interaction between the PL protein LPAP and the PDZ domain of TIP-1 is described. As the Office Action acknowledges, based upon this information and other information regarding the binding of LPAP with CD45, applicants have described a role for the TIP-1/LPAP interaction. The burden in an enablement rejection is on the Examiner to explain the reasons for concluding that the specification fails to describe how to make and use the claimed invention (see, e.g., MPEP 2164.04). Thus, having provided an explanation with regard to a role for the TIP-1/LPAP interaction in the specification, the burden is on the Examiner to provide a rationale for why this discussion is not deemed credible. The Examiner focuses on the certain issues regarding the function of LPAP prior to the filing of the instant application, rather than the function described in the specification. In this respect, it is further noted that certain claims (e.g., claims 19 and 20) specifically recite the nature of the biological activity that is affected by the inhibition of the TIP-1/LPAP interaction.

The third general reason set forth in the Office Action to support the assertion that the claims are not sufficiently enabled is that there is uncertainty regarding which PL sequences can bind the PDZ protein TIP-1. The Office Action first notes that the specification states that some, but not all, PL proteins having the general motif X-S/T-X2-V/I/L bind TIP-1. Because of this uncertainty it is concluded that undue experimentation would be required "to *predict* which agent, known or unknown, would be a mimetic of the carboxy terminus of the PL protein LPAP." Office Action at page 4 (emphasis added).

In response to this assertion, it is first submitted that the Office is applying an incorrect standard in evaluating whether undue experimentation is required. According to the Office Action, undue experimentation is required unless one of ordinary skill in the art can *predict* a priori whether a particular agent is effective in inhibiting the binding between LPAP

and TIP-1. This standard suggests that the Office is equating considerable experimentation with undue experimentation. In particular, it suggest the possibility that the Office considers the possibility that considerable experimentation may be involved to identify certain agents to constitute undue experimentation. This view, however, is contrary to established case law concerning this issue. As stated in *In re Wands*, 8 USPQ2d 1400, 858 F.2d 731, 737 (Fed. Cir. 1988):

> [E]xperimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art...*The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.* (emphasis added).

The requirement the Office Action imposes, namely that one be able to *predict* which agents have inhibitory activity, is at odds with the foregoing standard. Specifically, the standard set forth in the Office Action is too high. To require an ability to *predict* agents that would have the desired activity elevates the enablement standard to one in which NO experimentation is allowed.

The case law just cited, however, establishes a lower standard. The foregoing quotation evidences that *considerable experimentation* is permissible if *either* of two criteria are satisfied: 1) the experimentation is routine, OR 2) the specification provides guidance in the direction in which experimentation should proceed. It is submitted that although only one of these criteria need be satisfied, the instant application satisfies both.

Starting with the second of these criterion, the application discloses in Table 2 which of over 50 PL proteins were or were not able to bind the PDZ protein TIP-1. This extensive binding information provides one of ordinary skill significant guidance regarding active and inactive binding motifs. Moreover, the specification provides significant additional information to guide one of ordinary skill in the development of appropriate inhibitory agents, including: 1) strategies for identifying PL proteins that bind to any particular PDZ protein (see, e.g., pages 73-81); an analogous approach can be taken to identify inhibitors of a specific PDZ and PL interaction; 2) assays specifically designed to identify inhibitors of a particular PDZ and PL pair (e.g., TIP-1 and LPAP); and 3) examples that detail the strategy for developing inhibitors of particular PDZ and PL interactions (see, e.g. Examples 7 and 8). While these two examples are not specific for TIP-1 and LPAP, they nonetheless describe the general approach to be taken. The combination of specific binding information coupled with discussion on strategies for developing inhibitors provides guidance regarding specific motifs that could be used in the design of inhibitors and the guidance concerning any further experimentation that one might want to undertake. It is submitted that this is all that the law requires under criterion 2.

Turning to the first of the foregoing criterion, the instant application discloses several assays that can be utilized to determine whether any particular agent can inhibit the interaction between a PDZ and PL protein (here, TIP-1 and LPAP). These assays are described in general terms on pages 58-71 and were used to test over 2300 combinations of PDZ and PL proteins to detect binding (see, e.g., Table 2), thus evidencing the ability to use such assays as part of a rapid, high-throughput screen. As just noted, the use of these assays specifically within the context of screening for agents that inhibit a particular PDZ and PL pair are described at pages 84-90. Using these powerful screening techniques, it is submitted that one of ordinary skill could rapidly and routinely screen agents to identify those with the desired activity, thereby satisfying criterion 1.

So, to summarize, the specific binding data that is provided regarding motifs that can and cannot bind TIP-1 provide significant guidance regarding the structure that inhibitors of the TIP-1/LPAP interaction should have. The discussion and examples in the specification

regarding specific high-throughput assays that can be used to screen such designed compounds provides further guidance on how such compounds can be routinely screened to identify those with the desired activity. Thus, the specification satisfies not just one of the requisite criteria set forth above, but both.

While the foregoing reasons by themselves are deemed sufficient to address this third concern, the additional specific points made in the Office Action with respect to this issue are also addressed. The Office Action points to the statement in Table 6 that not all ligands having the consensus binding motif for TIP-1 (X-S/T-X2-V/I/L) bind TIP-1, suggesting in part a concern that the claims read on inoperative embodiments. The law is clear, however, that a claim can read on certain inoperative embodiments, provided one of ordinary skill could determine which embodiments were inoperative with no more effort than is normally required in the art (see, e.g., MPEP 2164.08(b) and Atlas Powder Co. v. E.I. du Pont de Nemours and Co., 750 F.2d 1569, 1577; 224 USPQ 409, 414 (Fed. Cir. 1984). For all the reasons just described, any inoperative embodiments could be readily identified using, for example, the assays that are described in the application.

It is also stated that undue experimentation would be required because certain claims require that the inhibitory agent be a peptide that shares only two or three residues from the carboxy-terminus of LPAP, whereas the binding motif is disclosed to be at least four amino acids in length. Applicants disagree. These claims refer to agents having specifically defined characteristics: 1) the agent must be a peptide, and 2) the peptide must include two or three residues from a motif of four amino acids that is known to bind the recited PDZ protein (i.e., TIP-1). In view of these specific limitations and the additional guidance and screening methods described above, one of ordinary skill could identify agents having the desired activity without undue experimentation.

The Office Action additionally states that the claims are not enabled because of a lack of examples describing inhibitors of TIP-1 and LPAP. In response it is reiterated that the application includes two examples that illustrate the general strategy that one would employ to identify an inhibitor of a particular PDZ and PL pair (see, e.g., Examples 7 and 8. Furthermore,

MPEP 2164.02 makes clear that the presence or absence of a working example is only one of many factors to consider when evaluating whether the enablement requirement has been satisfied.

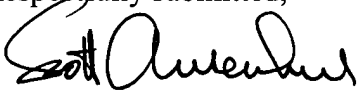
For all the reasons described above, it is submitted that the requirements for enablement have been satisfied. Accordingly, it is requested that this rejection be withdrawn.

IV. Rejection of Claims under 35 U.S.C. 112, Second Paragraph

Claims 1, 5-8 and 16-17 are rejected as being indefinite for reading on non-elected subject matter. The claims have been amended to address this issue.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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